HIV AND ILLICIT DRUG USERS (IDUs) (Updated January 10, 2011)

Treatment Challenges of HIV-Infected IDUs

Injection drug use is the second-most common mode of HIV transmission in the United States. In addition, noninjection illicit drug use may facilitate sexual transmission of HIV. Injection and noninjection illicit drugs include the following: heroin, cocaine, marijuana, and club drugs (i.e., methamphetamine, ketamine, gamma-hydroxybutyrate [GHB], and amyl nitrate). The most commonly used illicit drugs associated with HIV infection are heroin and stimulants (e.g., cocaine and amphetamines); however, the use of club drugs has increased substantially in the past several years and is common among those who have HIV infection or who are at risk of HIV infection. Methamphetamine and amyl nitrate (i.e., poppers) have been the most strongly associated with high-risk sexual behavior in men who have sex with men (MSM), and the association is less consistent with the other club drugs *[1]*.

All illicit drugs have been associated with depression and anxiety, either as part of the withdrawal process or as a consequence of repeated use. This is particularly relevant in the treatment of HIV infection because depression is one of the strongest predictors of poor adherence and poor treatment outcomes *[2]*. Although treatment of HIV disease in this population can be successful, IDUs who have HIV disease present special treatment challenges. These may include the following: (1) an array of complicating comorbid medical and mental health conditions; (2) limited access to HIV care; (3) inadequate adherence to therapy; (4) medication side effects and toxicities; (5) the need for substance abuse treatment; and (6) drug interactions that can complicate HIV treatment *[3]*.

Underlying health problems among injection and noninjection drug users result in increased morbidity and mortality, either independent of or accentuated by HIV disease. Many of these problems are the consequence of prior exposures to infectious pathogens from nonsterile needle and syringe use. Such problems can include hepatitis B or C virus infection, tuberculosis, skin and soft tissue infections, recurrent bacterial pneumonia, and endocarditis. Other morbidities such as alteration in levels of consciousness and neurologic and renal disease are not uncommon. Furthermore, these comorbidities are associated with a higher risk of drug overdoses in IDUs with HIV disease, due in part to respiratory, hepatic, and neurological impairments *[4]*. Successful HIV therapy for IDUs often rests upon acquiring familiarity with and providing care for these comorbid conditions and overdose prevention support.

IDUs have less access to HIV care and are less likely to receive antiretroviral therapy (ART) than other populations *[5-6]*. Factors associated with low rates of ART among IDUs include active drug use, younger age, female gender, suboptimal health care, recent incarceration, lack of access to rehabilitation programs, and lack of expertise among health care providers *[5-6]*. The typically unstable, chaotic life patterns of many IDUs; the powerful pull of addictive substances; and common misperceptions about the dangers, impact, and benefits of ART all contribute to decreased adherence *[7]*. The chronic and relapsing nature of substance abuse as a biologic and medical disease, compounded by the high rate of mental illness that antedates and/or is exacerbated by illicit substance use, additionally complicate the relationship between health care workers and IDUs *[8-9]*. The first step in provision of care and treatment for these individuals is to recognize the existence of a substance abuse problem. Whereas this is often open and obvious, patients may hide such behaviors from clinicians. Assessment of a patient for substance abuse should be part of routine medical history taking and should be done in a clinical, straightforward, and nonjudgmental manner.

Treatment Efficacy in HIV-Infected Illicit Drug Use Populations

Although IDUs are underrepresented in HIV therapy clinical trials, available data indicate that—when they are not actively using drugs— efficacy of ART in IDUs is similar to that seen in other populations *[10]*. Furthermore, therapeutic failure in this population generally correlates with the degree that drug use disrupts daily activities rather than with drug use *per se [11]*. Providers need to remain attentive to the possible impact these factors have upon the patient before and during prescription of ART. Although many IDUs can sufficiently control their drug use over long enough periods of time to benefit from care**,** substance abuse treatment is often necessary for successful HIV management.

Close collaboration with substance abuse treatment programs and proper support and attention to this population's special multidisciplinary needs are critical components of successful HIV treatment. Essential to this end are accommodating and flexible, community-based HIV care sites that are characterized by familiarity with and

nonjudgmental expertise in management of drug users' wide array of needs and in development of effective strategies to promote medication adherence *[9]*, including, if available, the use of adherence support mechanisms such as modified directly observed therapy, which has shown promise in this population *[12]*.

Antiretroviral Agents and Opioid Substitution Therapy

IDUs are more likely to experience an increased frequency of side effects and toxicities of ART. Although not systematically studied, this is likely because underlying hepatic, renal, neurologic, psychiatric, gastrointestinal, and hematologic disorders are highly prevalent among IDUs. Selection of ARV agents in this population should be made with consideration of these comorbid conditions. Opioid substitution therapies such as methadone and buprenorphine/naloxone and extended release naltrexone are commonly used for management of opioid dependence in HIV-infected patients.

Methadone and ART. Methadone, an orally administered, long-acting opioid agonist, is the most common pharmacologic treatment for opioid addiction. Its use is associated with decreased heroin use, decreased needle sharing, and improved quality of life. Because of its opioid-induced effects on gastric emptying and the metabolism of cytochrome P (CYP) 450 isoenzymes 2B6, 3A4, and 2D6, pharmacologic effects and interactions with ARV agents may commonly occur *[13]*. These may diminish the effectiveness of either or both therapies by causing opioid withdrawal or overdose, increased methadone toxicity, and/or decreased ARV efficacy. Efavirenz (EFV), nevirapine (NVP), and lopinavir/ritonavir (LPV/r) have been associated with significant decreases in methadone levels. It is necessary to inform patients and substance abuse treatment facilities of the likelihood of this interaction. The clinical effect is usually seen after 7 days of coadministration and may be managed by increasing the methadone dosage, usually in 5-mg to 10-mg increments daily until the desired effect is achieved.

Buprenorphine and ART. Buprenorphine, a partial μ-opioid agonist, is administrated sublingually and is often coformulated with naloxone. It is being increasingly used for opioid dependence treatment. The lower risk of respiratory depression and overdose compared with methadone allows it to be prescribed by physicians in primary care for the treatment of opioid dependency. This flexible treatment setting could be of significant value to opioid-addicted HIV-infected patients who require ART because it enables one physician or program to provide both medical and substance abuse services. Limited information is currently available about interactions between buprenorphine and antiretroviral agents *[13-14]*. Findings from available studies show a more favorable drug interaction profile than that of methadone.

Naltrexone and ART. A once monthly extended-release intramuscular formulation of naltrexone was recently approved for prevention of relapse in patients who have undergone an opioid detoxification program. Naltrexone is also indicated for treatment of alcohol dependency. Naltrexone is not metabolized via the CYP 450 enzyme system and is not expected to interact with protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) *[15]*.

Table 11 provides the currently available pharmacokinetic interaction data that clinicians can use as a guide for managing patients receiving ART and methadone or buprenorphine. Particular attention is needed concerning communication between HIV care providers and drug treatment programs regarding additive drug toxicities and drug interactions resulting in opiate withdrawal or excess.

Methylenedioxymethamphetamine (MDMA), GHB, ketamine, and methamphetamine all have the potential to interact with ARV agents because all are metabolized, at least in part, by the CYP 450 system. Overdoses secondary to interactions between the party drugs (i.e., MDMA or GHB) and PI-based ART have been reported *[16]*.

Summary

It is usually possible over time to support most active drug users such that acceptable adherence levels with ARV agents can be achieved *[17-18]*. Providers must work to combine all available resources to stabilize an active drug user in preparation for ART. This should include identification of concurrent medical and psychiatric illnesses, drug treatment, needle and syringe exchange, reduction in high-risk sexual behavior, and harm reduction strategies. A

history of drug use alone is insufficient reason to withhold ART because individuals with a history of prior drug use have adherence rates similar to individuals who do not abuse drugs.

Important considerations in the selection of successful regimens and the provision of appropriate patient monitoring in this population include supportive clinical sites; linkage to substance abuse treatment; and awareness of the interactions between illicit drugs and ARV agents, including the increased risk of side effects and toxicities. Simple regimens should be considered to enhance medication adherence. Preference should be given to ARV agents that have a lower risk of hepatic and neuropsychiatric side effects, simple dosing schedules, and minimal interaction with methadone.

Table 11. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction (January 10, 2011)

Concomitant Drug	Antiretroviral Class/Drug	Pharmacokinetic Interactions Recommendations/Clinical Comments
Buprenorphine	EFV	buprenorphine AUC ↓ 50%; norbuprenorphine* AUC ↓ 71% No withdrawal symptoms reported. No dosage adjustment recommended; however, monitor for withdrawal symptoms.
	ATV	buprenorphine AUC ↑ 93%; norbuprenorphine AUC ↑ 76%; ↓ ATV levels possible Do not coadminister buprenorphine with unboosted ATV.
	ATV/r	buprenorphine AUC ↑ 66%; norbuprenorphine AUC ↑ 105% Monitor for sedation. Buprenorphine dose reduction may be necessary.
	DRV/r	buprenorphine: no significant effect, norbuprenorphine AUC ↑ 46% and C_{min} ↑ 71% No dose adjustment necessary.
	TPV/r	buprenorphine: no significant effect; norbuprenorphine AUC, C_{max}, and C_{min} ↓ 80%; TPV C_{min} ↓ 19%–40% Consider monitoring TPV level.
	3TC, ddI, TDF, ZDV, NVP, LPV/r, NFV	No significant effect No dosage adjustment necessary.
	ABC, d4T, FTC, ETR, FPV +/- RTV, IDV +/- RTV, SQV/r, RAL, MVC, T20	No data

Table 11. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction

Concomitant Drug	Antiretroviral Class/Drug	Pharmacokinetic Interactions Recommendations/Clinical Comments
Methadone	ABC	methadone clearance ↑ 22% No dosage adjustment necessary.
	d4T	d4T AUC ↓ 23% and C_{max} ↓ 44% No dosage adjustment necessary.
	ZDV	ZDV AUC ↑ 29%–43% Monitor for ZDV-related adverse effects.
	EFV	methadone AUC ↓ 52% Opioid withdrawal common; increased methadone dose often necessary.
	NVP	methadone AUC ↓ 41% NVP: no significant effect Opioid withdrawal common; increased methadone dose often necessary.
	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	With ATV/r, DRV/r, FPV/r: R-methadone[†] AUC ↓ 16%–18%; With LPV/r: methadone AUC ↓ 26%–53%; With SQV/r 1,000/100mg BID: R-methadone AUC ↓ 19%; With TPV/r: R-methadone AUC ↓ 48% Opioid withdrawal unlikely but may occur. No adjustment in methadone usually required; however, monitor for opioid withdrawal and increase methadone dose as clinically indicated.
	FPV	No data with FPV (unboosted) With APV: R-methadone C_{min} ↓ 21%, AUC no significant change Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
	NFV	methadone AUC ↓ 40% Opioid withdrawal rarely occurs. Monitor and titrate dose as clinically indicated. May require increased methadone dose.
	ddI (EC capsule), 3TC, TDF, ETR, RTV, ATV, IDV, RAL	No significant effect No dosage adjustment necessary.
	FTC, MVC, T20	No data

[*] Norbuprenorphine is an active metabolite of buprenorphine.
[†] R-methadone is the active form of methadone.

Acronyms: 3TC = lamivudine, d4T = stavudine, T20 = enfuvirtide, ABC = abacavir, APV = amprenavir, ATV = atazanavir, ATV/r = atazanavir/ritonavair, ddI = didanosine, DRV/r = darunavir/ritonavir, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, IDV = indinavir, IDV/r = indinavir/ritonavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NVP = nevirapine, RAL = raltegravir, RTV = ritonavir, SQV/r = sacquinavir/ritonavir, TDF = tenofovir, TPV = tipranavir, TPV/r = tipranavir/ritonavir, ZDV = zidovudine

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